REMARKS

Claims 1-4 are currently pending in the application. The foregoing separate sheets marked as "Listing of Claims" shows all the claims in the application, with an indication of the current status of each.

Priority.

Examiner states that although the filing papers for the present application state an intention to claims priority to Provisional Application No. 60/232,060, no statement to that effect is included in the first sentence of the specification.

Applicant hereby amends the specification to include a sentence stating that priority is claimed to the Provisional Application.

In view of the foregoing, Applicant respectfully request entry of the amendment to the specification, and submits that compliance with conditions for receiving the benefit of an earlier filing date have thereby been met.

35 USC § 112 Rejection

Claim 2 stands rejected under 35 USC § 112 as failing to comply with the written description requirement. The Examiner states that the claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor was had possession of the claimed invention at the time of filing. Examiner further states that "The specification does not described binding determinant residues that contribute in excess of about 100 cal/mol to the Gibbs energy of binding."

Applicant respectfully disagrees. On page 12, lines 5-8, the embodiment of the invention recited in claim 2 is described as follows: "Those residues that contribute the most to the Gibbs energy of binding define the binding determinants of the binding site, i.e. *those residues that contribute more than about 100 cal/mol to the Gibbs energy of binding.*" The process of selecting the residues for which the Gibbs energy must be calculated is described earlier in the specification (see page 11, lines 20, to page 12, line7). Once selected, "The contribution of each individual residue to the Gibbs energy of binding is calculated by applying a parameterized Gibbs energy function..." (Page 11, lines 27-29). Further, "The calculation of the Gibbs energy of

binding permits prediction of ... the contribution of each residue to the binding affinity" (page 12, lines 4-5). Thus, the rationale and means for calculating the Gibbs energy of binding are clearly given. Once calculated, it is necessary only to select those residues which "define the binding determinants" (page 12, line 6). Applicant submits that the criterion is set forth clearly: residues are selected if they contribute more than about 100 cal/mol to the Gibbs energy of binding, the actual amount that they contribute being calculated as described. It is not possible to "describe binding determinant residues that contribute in excess of about 100 cal/mol to the Gibbs energy of binding" because there is not one set of amino acid residues that does so. The residues that do so will vary from protein to protein, and will also depend on which ligand is binding to the protein. The residues that contribute in excess of about 100 cal/mol to the Gibbs energy of binding will be selected anew for each protein that is analyzed according to the methods of the present invention, and Applicant submits that the means for doing so is adequately and painstakingly set forth in the specification.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of this rejection.

35 USC §102(b) Rejection

Claims 1, 3 and 4 stand rejected under 35 USC §102(b) as anticipated by Friere. The Examiner states that the claims are drawn to methods of displaying models of a molecule in which the residues of the molecule that are affected by binding of a ligand are highlighted, and computer programs that execute the method. Examiner further states that Figure 3 of Freire shows the results of an analysis of ligand binding in which the residues that are affected by the binding are highlighted, and discusses the program Core_Bind throughout.

Applicant respectfully disagrees with Examiner's equating the method used in Freire to that of the present invention. It is true that the two methods have a similar goal of predicting the effects of binding a ligand at distal parts of a molecule that are not directly involved in binding. However, as described at length in the present application, all previous methods for doing so (which would include that described by Freire) are able to deal only with relatively small molecules. For example, in the Freire publication, the protein that is analyzed is lysozyme, which contains only 129 amino acids and has a molecular weight of 14 kDa. This is because the

analysis performed in Freire is an exhaustive enumeration of the states of the molecule, and such an analysis is within the reach of available computing power.

In contrast, the methods of the present invention provide means to predict the effects of ligand binding at distal sites on very large molecules, e.g. those for which an exhaustive enumeration would involve a prohibitively large number of calculations. See the discussion concerning the problem solved by the present invention on page 6, lines 25-29 and page 7, lines 21-22. This is accomplished by generating a "subset" of all possible conformations of the molecule, a "conformational ensemble". The conformational ensemble is comprised of many (but not all) conformational states of the molecule. The number of states will vary from molecule to molecule, and will also depend on the ligand being investigated, but there is a distinct criterion for determining how many states are included: the conformational ensemble is comprised of a number of conformational states of the molecule sufficient to achieve convergence to a stable ensemble average. This step of the method is recited in step two of claim 2: "...generating, using the processor, a conformational ensemble for said molecule, wherein said conformational ensemble is comprised of a number of conformational states of said molecule sufficient to achieve convergence to a stable ensemble average...". Applicant notes that this step of generating a conformational ensemble is not present in the methodology described by the cited Freire reference, which employs an exhaustive enumeration of **all** states of the molecule.

A detailed description of the conformational ensemble and the means of generating the ensemble, are given in the specification beginning on page 6, line 25, through page 8, line 3. Briefly, a high-resolution structure is selected as a template or native state, and a random sampling algorithm selects a group of residues (window size typically 4-12 residues) of the template and the conformation of the residues in the selected group is switched to a defined reference state such as the unfolded conformation. For a large protein (e.g. in excess of 150 residues, at least about 20,000 states with a degree of unfolding not to exceed 0.5 are generated, as this is typically sufficient to achieve convergence to a stable ensemble average. Applicant notes that, if necessary, more states may be generated to achieve convergence, but in any case, an exhaustive enumeration is not required. Further calculations (e.g. calculation of residue-level stability constant, residue-level probabilities, etc.) are carried out to finally arrive at the identification of residues that are affected by the binding of a ligand, based on the manageable

number of states in the ensemble. Surprisingly, the inventors have discovered that the affected residues can be accurately identified using this method even though it does not involve exhaustive computations for each conformation of each residue in the molecule.

Applicant submits that the methods described in the Freire reference do not include the generation of a conformational ensemble and thus do not anticipate claims 1, 3 and 4 of the present invention.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Closing Comments and Formal Matters

In view of the foregoing, it is requested that the application be reconsidered, that claims 1-4 be allowed, and that the application be passed to issue.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at 703-787-9400 (fax: 703-787-7557; email: ruth@wcc-ip.com) to discuss any other changes deemed necessary in a telephonic or personal interview. Please charge any deficiencies in fees and credit any overpayment of fees to Attorney's Deposit Account No. 50-2041.

Respectfully submitted,

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